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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/12, A61K 31/44, C07D 401/14 | A1

(11) International Publication Number: WO 98/52943

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/EP98/02992

(22) International Filing Date: 13 May 1998 (13.05.98)

(30) Priority Data:
9710523.3 23 May 1997 (23.05.97) GB

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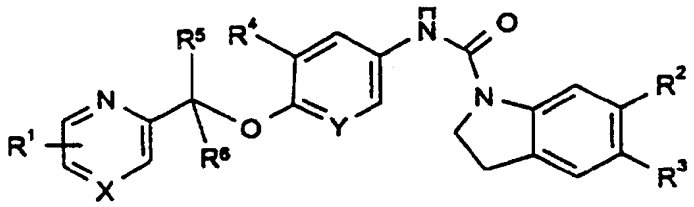
(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INDOLINE DERIVATIVES AS $5HT_{2C}$ RECEPTOR ANTAGONISTS

(57) Abstract



(I)

A compound of formula (I) or a salt thereof, wherein: R^1 is hydrogen or C_{1-6}alkyl; R^2, R^3 and R^4 groups are independently hydrogen, halogen or C_{1-6}alkyl optionally substituted by one or more fluorine atoms. R^5 and R^6 groups are independently hydrogen or C_{1-6}alkyl; X and Y are independently CH or nitrogen, provided that X is nitrogen when Y is nitrogen and both R^5 and R^6 are hydrogen. The compounds exhibit enhanced $5HT_{2C}$ receptor antagonist activity profile. $5HT_{2C}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimer's disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of glaucoma, certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome) as well as microvascular diseases such as macular oedema and retinopathy.

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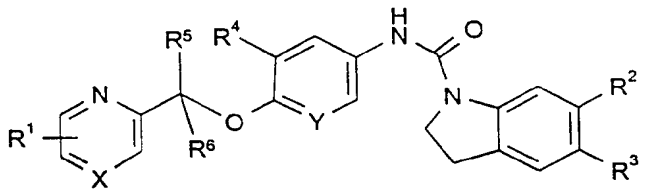
INDOLINE DERIVATIVES AS 5HT2C RECEPTOR ANTAGONISTS

This invention relates to indoline derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

PCT/EP96/00368 (WO96/23783), PCT/EP97/03156 (WO97/48699) and PCT/EP97/03157 (WO97/48700) disclose indoline derivatives which are described as possessing $5HT_{2C/2B}$ receptor antagonist activity. A novel class of compounds has now been discovered which fall within the generic scope of PCT/EP96/00368, but are not specifically dosclosed therein, and have been found to exhibit a surprisingly enhanced $5HT_{2C}$ receptor antagonist activity profile. $5HT_{2C}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of glaucoma, certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome) as well as microvascular diseases such as macular oedema and retinopathy.

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



(I)

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3 and R^4 groups are independently hydrogen, halogen or C_{1-6} alkyl optionally substituted by one or more fluorine atoms;

R^5 and R^6 groups are independently hydrogen or C_{1-6} alkyl:

X and Y are independently CH or nitrogen, provided that X is nitrogen when Y is nitrogen and both R^5 and R^6 are hydrogen;

C_{1-6} Alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Preferably R^1 is hydrogen.

Suitably R^2, R^3 and R^4 groups are independently hydrogen, halogen or C_{1-6} alkyl optionally substituted by one or more fluorine atoms. Preferably R^2 is C_{1-6} alkyl substituted by one or more fluorine atoms, particularly CF_3 and R^3 is C_{1-6} alkyl, particularly methyl. Preferably R^4 is hydrogen or C_{1-6} alkyl, preferably R^4 is hydrogen.

R^5 and R^6 groups are independently hydrogen or C_{1-6}alkyl, in particular methyl.

Particular compounds of the invention include:

5-Methyl-1-[4-(pyridin-2-ylmethyloxy)phenylcarbamoyl]-6-trifluoromethylindoline,

5-Methyl-1-[2-(pyrazin-2-ylmethyloxy)pyridin-5-yl-carbamoyl]-6-trifluoromethylindoline,

5-Methyl-1-[2-(1-pyridin-2-ylethoxy) pyridin-5-yl-carbamoyl]-6-trifluoromethylindoline,

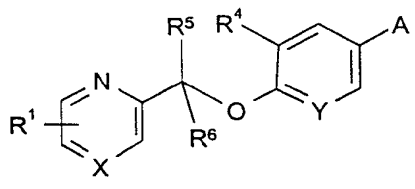
and pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

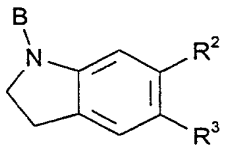
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The compounds of the invention can be prepared using standard procedures such as those of PCT/EP96/00368 (WO96/23783), for example by the coupling of a compound of formula (II);



(II)

in which R^1, R^4, R^5 , R^6, X and Y are as defined in formula (I) with a compound of formula (III);



(III)

in which R^2 and R^3 and are as defined in formula (I) and A and B contain the appropriate functional group(s) necessary to form the moiety -NHCO when coupled and thereafter optionally forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and B include:

(i) A is -N=C=O and B is hydrogen,

(ii) A is -NHCOL and B is hydrogen,

(iii) A is $-NH_2$ and B is COL, or

(iv) A is halogen and B is $-CONH_2$

wherein L is a leaving group. Examples of suitable leaving groups L include halogen such as chloro or bromo, imidazole, or phenoxy or phenylthio optionally substituted, for example, with one or more halogens.

Compounds of formula (II) and (III) may be prepared according to known methods or analogous to known methods, for example using the procedures described in WO 95/01976 and PCT/EP96/00368 (WO96/23783).

Novel intermediates of formula (II) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2C}$ receptor antagonist activity and are believed to be of potential use for the treatment or prophylaxis of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders (including disturbances of Circadian rhythym), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also

expected to be of use in the treatment of glaucoma, certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the

stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

1-Methoxy-4-nitro-2-trifluoromethylbenzene (D1)

Sodium (11.78g, 0.512 mol) was dissolved in dry methanol (1l) and to the resulting solution was added a solution of 1-chloro-4-nitro-2-trifluoromethyl-benzene (96.22g, 0.427 mol) in methanol (100 ml). The reaction mixture was refluxed for 3 h then cooled and evaporated *in vacuo*. The residue was partitioned between water (500 ml) and dichloromethane (3 x 400 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the title compound (93.76g, 99%) as a white solid. ^1H NMR ($CDCl_3$) δ: 4.05 (3H, s), 7.12 (1H, d), 8.45 (1H, dd), 8.52 (1H, d).

Description 2

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D2)

A mixture of 1-methoxy-4-nitro-2-trifluoromethylbenzene (D1) (93g, 0.421 mol) and 4-chlorophenoxyacetonitrile (77.55g, 0.463 mol) in dry DMF (500 ml) was added dropwise over 0.75 h to a stirred solution of KO^tBu (103.85g, 0.927 mol) in dry DMF

(400 ml) at -10° C. After complete addition the resulting purple solution was maintained at -10° C for 1 h then poured into a mixture of ice/water (1.5 l) and 5 M aqueous HCl (1.5 l). The resulting mixture was extracted with dichloromethane (3 x 1 l). The combined extracts were washed with water (3 l), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica using 10-40% ethyl acetate/petroleum ether as eluant to give the crude product which was recrystallised from ethyl acetate/petroleum ether to afford the title compound (85.13g, 78%) as a white solid, m.p. 103-104 °C.

^1H NMR ($CDCl_3$) δ: 4.10 (3H, s), 4.37 (2H, s), 7.34 (1H, s), 8.53 (1H, s).

Description 3

5-Methoxy-6-trifluoromethylindole (D3)

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D2) (85g, 0.327 mol) in ethanol/water (9:1, 1.6 l) and glacial acetic acid (16 ml) was hydrogenated over 10% palladium on carbon (50 g) at 50 psi for 0.5 h at room temperature. The reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between aqueous K_2CO_3 (1 l) and dichloromethane (2 x 1 l) and the combined organic extract was dried (Na_2SO_4) and evaporated to afford the title indole (67.63g, 96%) as a grey solid.

^1H NMR ($CDCl_3$) δ: 3.94 (3H, s), 6.53 (1H, m), 7.21 (1H, s), 7.32 (1H, m), 7.64 (1H, s), 8.25 (1H, br s).

Description 4

5-Methoxy-6-trifluoromethylindoline (D4)

The indole (D3) (67.63g, 0.315 mol) in glacial acetic acid (500 ml) was treated with sodium cyanoborohydride (40 g, 0.637 mol) portionwise at room temperature with stirring. After 3 h at room temperature the reaction mixture was diluted with water (500 ml) and basified with 40% aqueous NaOH with cooling. The mixture was then extracted with dichloromethane (3 x 500 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to give the title compound (67.73g, 99%) as an off-white solid.

^1H NMR ($CDCl_3$) δ: 3.07 (2H, t), 3.58 (2H, t), 3.67 (1H, br s), 3.83 (3H, s), 6.83 (1H, s), 6.88 (1H, s).

Description 5

5-Hydroxy-6-trifluoromethylindoline (D5)

A mixture of 5-methoxy-6-trifluoromethylindoline (D4, 7.5g, 34.3 mmol) and iodotrimethylsilane (12.5 ml, 89.3 mmol) in dry chloroform (70 ml) was heated under

reflux for 65 h. Methanol was then added cautiously with stirring to the cooled mixture, and solvent was then removed *in vacuo*. The residue was treated with saturated sodium bicarbonate solution and water until basic, and then extracted with dichloromethane/methanol. The organic extract was washed with brine, dried and evaporated. The residue was extracted with ether in a Soxhlet apparatus, and concentration of the resultant solution gave the title compound in three crops (total 2.85g, 41%), m.p. > 180° (decomp.).

^{1}H NMR ($CDCl_3/CD_3OD$) δ: 3.02 (2H, d, J=8), 3.52 (2H, d, J=8), 4.00 (3H, s), 6.77 (1H, s), 6.83 (1H, s).

Description 6

1-Acetyl-5-hydroxy-6-trifluoromethylindoline (D6)

A mixture of indoline (D5, 2.84g, 14 mmol) and acetic anhydride (1.32 ml, 14 mmol) in dry dichloromethane (50 ml) was stirred at room temperature for 3h, then evaporated. The residue was treated cautiously with saturated sodium bicarbonate solution, then the solid product was filtered off, washed with water and dried to give the title compound (3.28g, 96%), m.p. 244-7°C.

^{1}H NMR (d_6-DMSO) δ: 2.10 (3H, s), 3.11 (2H, t, J=8), 4.06 (2H, t, J=8), 6.88 (1H, s), 8.18 (1H, s).

Description 7

1-Acetyl-6-trifluoromethyl-5-trifluoromethylsulphonyloxy-indoline (D7)

To a solution of the acetylindoline (D6, 1.19g, 4.9 mmol) in dry pyridine (10 ml) at 0°C was added trifluoromethanesulphonic anhydride (1.52g, 5.4 mmol). The mixture was then stirred overnight, while slowly warming to room temperature. The mixture was partially evaporated, the residual liquor was diluted well with water and the precipitate was filtered off. The crude product was dissolved in dichloromethane and the solution was washed with 1N hydrochloric acid and brine, dried and evaporated to give the title compound (1.77g, 96%).

^{1}H NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.32 (2H, t, J=8), 4.19 (2H, t, J=8), 7.29 (1H, s), 8.60 (1H, s).

MS m/z = 378 (MH^+)

Description 8

5-Methyl-6-trifluoromethylindoline (D8)

To a mixture of the trifluoromethylsulphonyloxyindoline (D7, 1.77g, 4.69 mmol), lithium chloride (0.60g, 14.1 mmol) and bis(triphenylphosphine) palladium (II) chloride (0.10g, 0.14 mmol) in dry dimethylformamide (15 ml) was added

tetramethyltin (0.72 ml, 5.2 mmol). The mixture was heated at 110°C for 3.5h, then cooled and evaporated. The residue was partitioned between dichloromethane and water, and the organic phase was washed with brine, dried and evaporated. The crude product was dissolved in ethanol (30 ml), 10% aqueous sodium hydroxide solution (7.5 ml) and solid sodium hydroxide (1g) were added and the mixture was heated under reflux overnight. Ethanol was removed *in vacuo*, and the residue was diluted with water and extracted with dichloromethane. The organic extract was washed with brine, dried and evaporated. The residue was chromatographed on silica gel (50g), eluted under suction with 2:1 ether/petroleum ether to give the title compound (0.70g, 74%), m.p. 43-4°C.

^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.02 (2H, t, J=8), 3.57 (2H, t, J=8), 3.78 (1H, broad), 6.85 (1H, s), 7.00 (1H, s).

Description 9

2-(4-Nitrophenoxy)methylpyridine (D9)

2-Pyridylcarbinol (5.45g, 50 mmol) was added dropwise to a stirred suspension of sodium hydride (80% in oil, 1.65g, 55 mmol) in dry dimethylformamide (DMF, 40 ml) at -20°C. The mixture was stirred at this temperature for 2h, then 4-fluoronitrobenzene (7.05g, 50 mmol) in DMF (10 ml) was added. The mixture was stirred overnight while warming slowly to room temperature. DMF was removed *in vacuo* and the residue was partitioned between dichloromethane/methanol and water. The organic phase was washed with water and brine, dried and evaporated. Recrystallisation of the residue from ether gave the title compound (3.55g, 31%), m.p. 37-8°C.

Description 10

2-(4-Aminophenoxy)methylpyridine (D10)

A solution of the nitrophenoxymethylpyridine (D9, 3.54g, 15.4 mmol) in ethanol (250 ml) was treated with a solution of tin (II) chloride (14.4g, 73.2 ml) in conc. HCl (25 ml) at 60°C for 2.5 h. The ethanol was removed *in vacuo* and the residue was partitioned between 10% aqueous sodium hydroxide and dichloromethane. The organic extract was washed with water and brine, dried and evaporated to give the title compound (2.76g, 90%) as a gum which on standing gave a solid, m.p. 62-5°C.

Description 11

5-Nitro-2-(pyrazin-2-ylmethyloxy)pyridine (D11)

Pyrazinemethanol (2.9g, 0.026 mole) in dry dimethylformamide (50 ml) was cooled to -20°C and treated portionwise with an 80% dispersion of sodium hydride in mineral

oil (1.03g, 0.034 mole) under argon. The mixture was stirred at -20°C for two hours. 2-Chloro-5-nitropyridine (3.34g, 0.021 mole) was added and the mixture was stirred at -20°C for 0.5 hour then warmed to room temperature and stirred for 2 hours. Water (2 ml) was added dropwise and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane, washed with 10% aqueous sodium hydroxide solution followed by water, dried (Na_2SO_4) and evaporated *in vacuo* to afford a solid residue which was filtered through a plug of silica using ethyl acetate as eluant to afford the title compound (4.9g, 100%) as an orange solid.
^1H NMR (250 MHz; $CDCl_3$) δ (ppm): 5.66 (2H, s), 6.99 (1H, d, J=8), 8.42 (1H, dd, J=8, 2), 8.61-8.64 (2H, m), 8.77 (1H, s), 9.08 (1H, d, J=2).

Description 12

5-Amino-2-(pyrazin-2-ylmethloxy)pyridine (D12)

5-Nitro-2-(pyrazin-2-ylmethyloxy)pyridine (D11, 2.0g, 0.0086 mole) in ethanol (80 ml) was treated with tin (II) chloride (8.3g, 0.044 mole) in conc. HCl (8 ml). The mixture was heated to 60°C for 1 hour. After cooling to room temperature, the mixture was diluted with water, basified with 10% aqueous sodium hydroxide solution, extracted into dichloromethane, dried (Na_2SO_4) and evaporated *in vacuo* to a gum which was purified by chromatography on silica gel, eluting with ethyl acetate, to afford the title compound (0.74g, 45%) as a pale yellow solid.
^1H NMR (200 MHz; $CDCl_3$) δ (ppm): 3.4 (2H, br s), 5.48 (2H, s), 6.73 (1H, d, J=8), 7.07 (1H, dd, J=3,8), 7.62 (1H, d, J=2), 8.49 (1H, d, J=2), 8.57 (1H, m), 8.76 (1H, s).

Description 13

Phenyl N-[2-(pyrazin-2-ylmethyloxy)pyridin-5-yl]carbamate (D13)

5-Amino-2-(pyrazin-2-ylmethyloxy)pyridine (D12, 0.73g, 0.0036 mole) in dichloromethane (40 ml) was cooled to -78°C under argon. Triethylamine (0.5ml, 0.0036 mole) was added, followed dropwise by phenyl chloroformate (0.5 ml, 0.0040 mole) and the mixture was warmed to room temperature over 2 hours, poured into aq. Na_2CO_3 (50 ml) and extracted with dichloromethane (3x50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave the title compound (1.05g) as a solid which was used without further purification.

Description 14

5-Nitro-2-(1-pyridin-2-ylethoxy)pyridine (D14)

1-Pyridin-2-ylethanol (2.0g, 0.016 mole) in dry dimethylformamide (40 ml) was cooled to -10°C and treated portionwise with an 80% dispersion of sodium hydride in mineral oil (0.5g, 0.017 mole) under argon. The mixture was stirred at -10°C for two

hours. 2-Chloro-5-nitropyridine (2.58g, 0.016 mole) was added and the mixture was stirred at -10°C for 0.5 hour then warmed to room temperature and stirred for 2 hours. Water (2 ml) was added dropwise and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane, washed with 10% aqueous sodium hydroxide solution followed by water, dried (Na_2SO_4) and evaporated *in vacuo* to afford a solid residue which was chromatographed on silica using ethyl acetate as eluant to afford the title compound (1.15g, 29%) as an orange solid.

^1H NMR (250 MHz; $CDCl_3$) δ (ppm): 1.73 (3H, d, J=7), 6.32 (1H, q, J=7), 6.95 (1H, d, J=8), 7.21 (1H, m), 7.40 (1H, d, J=8), 7.69 (1H,m), 8.38 (1H, dd, J=8, 2), 8.61 (1H, m), 9.02 (1H, d, J=2).

Description 15

5-Amino-2-(1-pyridin-2-ylethoxy)pyridine (D15)

5-Nitro-2-(1-pyridin-2-ylethoxy)pyridine (D14, 1.142g, 0.0047 mole) in ethanol (30 ml) was treated with tin (II) chloride (4.32g, 0.023 mole) in conc. HCl (8 ml). The mixture was heated to 60°C for 1 hour. After cooling to room temperature, the mixture was diluted with water, basified with 10% aqueous sodium hydroxide solution, extracted into dichloromethane, dried (Na_2SO_4) and evaporated *in vacuo* to a gum which was purified by chromatography on silica gel, eluting with ethyl acetate, to afford the title compound (0.54g, 54%) as a pale yellow oil.

Example 1

5-Methyl-1-[4-(pyridin-2-ylmethyloxy)phenylcarbamoyl]-6-trifluoromethylindoline

A mixture of the 2-(4-Aminophenoxy)methylpyridine (D10, 0.30g, 1.5 mmol), phenyl chloroformate (0.19 ml, 1.5 mmol) and triethylamine (0.20 ml, 1.5 mmol) in dry dichloromethane (20 ml) was stirred at room temperature for 2.25 h, then evaporated. The residue was suspended in dry acetonitrile. The indoline (D8 , 0.30g, 1.5 mmol) and triethylamine (0.20 ml, 1.5 mmol) were added and the mixture was heated at 100°C for 1.5h. After cooling, the mixture was poured into water and the precipitate was filtered off, washed with water and dried. Recrystallisation of the crude product from dichloromethane gave the title compound (0.35g, 55%), m.p. 176-8°C.

M.S. m/z = 428 (MH^+)

Example 2

5-Methyl-1-[2-(pyrazin-2-ylmethyloxy)pyridin-5-yl-carbamoyl]-6-trifluoromethylindoline (E2)

A mixture of indoline (D8, 0.73g, 3.61 mmol), phenylcarbamate (D13, 1.05g) and triethylamine (2 ml) in dry dimethylformamide (25 mL) was heated at 100°C for 3 hours. After cooling the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane, washed with 10% aqueous sodium hydroxide solution, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel eluting with ethyl acetate to afford the title compound (0.52g, 33%) as a white solid, m.p. 215-218°C.

NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.28 (2H, t, J=8), 4.12 (2H, t, J=8), 5.52 (2H, s), 6.31 (1H, s), 6.90 (1H, d, J=8), 7.08 (1H, s), 7.91 (1H, dd, J=8,2), 8.03 (1H, d, J=2), 8.22 (1H, s), 8.51 (1H, d, J=1), 8.58 (1H, m), 8.76 (1H, s).

Example 3

5-Methyl-1-[2-(1-pyridin-2-ylethoxy)pyridin-5-yl-carbamoyl]-6-trifluoromethylindoline (E3)

5-Amino-2-(1-pyridin-2-ylethoxy)pyridine (D15, 0.54g, 0.0025 mol) in dichloromethane (30 ml) and triethylamine (0.4 ml) was treated with phenyl chloroformate (0.31 ml, 0.0025 mol) dropwise at -30°C. and the mixture was warmed to room temperature over 2 hours, poured into aq. Na_2CO_3 (50 ml) and extracted with dichloromethane (3x50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave the carbamate as an oil. This crude material was treated with the indoline (D8, 0.50g, 0.0025 mol), triethylamine (1 ml) in dry dimethylformamide (25 ml) at 100°C for 1 hour. After cooling the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane, washed with 10% aqueous sodium hydroxide solution, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel eluting with ethyl acetate to afford the title compound (0.52g, 47%) as a white solid, m.p. 185-187°C.

^1H NMR (250 MHz; d_6DMSO) δ (ppm): 1.60 (3H, d, J=7), 2.38 (3H, s), 3.23 (2H, t, J=8), 4.13 (2H, t, J=8), 6.10 (1H, q, J=7), 6.90 (1H, d, J=8), 7.23 (1H, s), 7.28 (1H, m), 7.40 (1H, d, J=8), 7.75 (1H,m), 7.88 (1H, dd, J=8, 2), 8.14 (2H, m), 8.55 (1H, m), 8.62 (1H, s).

Pharmacological data

[^{3}H]-mesulergine binding to rat or human 5-HT_{2C} clones expressed in 293 cells in vitro

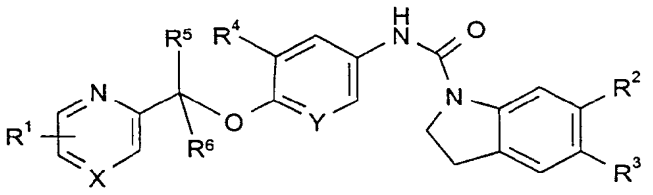
Compounds can be tested following the procedure outlined in WO 94/04533.

Reversal of MCPP-induced Hypolocomotion

Compounds can be tested following the procedure outlined in WO 94/04533.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3 and R^4 groups are independently hydrogen, halogen or C_{1-6} alkyl optionally substituted by one or more fluorine atoms.

R^5 and R^6 groups are independently hydrogen or C_{1-6} alkyl:

X and Y are independently CH or nitrogen, provided that X is nitrogen when Y is nitrogen and both R^5 and R^6 are hydrogen;

2. A compound according to claim 1 in which R^1 is hydrogen.

3. A compound according to claim 1 or 2 in which R^2 is CF_3.

4. A compound according to any one of claims 1 to 3 in which R^3 is methyl.

5. A compound according to any one of claims 1 to 4 in which R^4 is hydrogen.

6 A compound according to claim 1 which is:

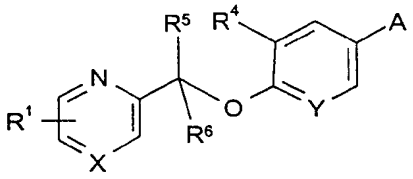
5-Methyl-1-[4-(pyridin-2-ylmethyloxy)phenylcarbamoyl]-6-trifluoromethylindoline,

5-Methyl-1-[2-(pyrazin-2-ylmethyloxy)pyridin-5-yl-carbamoyl]-6-trifluoromethylindoline,

5-Methyl-1-[2-(1-pyridin-2-ylethoxy) pyridin-5-yl-carbamoyl]-6-trifluoromethylindoline,

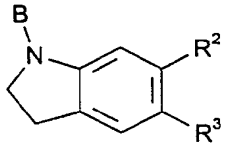
and pharmaceutically acceptable salts thereof.

7 A process for the preparation of a compound of formula (I) which comprises the reaction of a compound of formula (II)



(II)

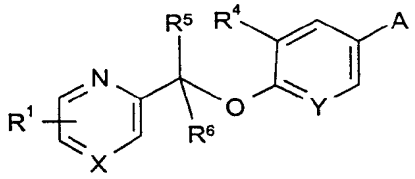
in which R^1, R^4, R^5 , R^6, X and Y are as defined in formula (I) with a compound of formula (III);



(III)

in which R^2 and R^3 and are as defined in formula (I) and A and B contain the appropriate functional group(s) necessary to form the moiety -NHCO when coupled and thereafter optionally forming a pharmaceutically acceptable salt thereof.

8. A compound of formula (II)



(II)

in which R^1, R^4, R^5 , R^6, X and Y are as defined in formula (I) and A is a group -N=C=O, NHCOL where L is a leaving group, NH_2 or halogen.

9. A compound according to any one of claims 1 to 6 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

11. Use of a compound according to any one of claims 1 to 6 for the manufacture of a medicament for the treatment of anxiety and/or depression.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02992

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 A61K31/44 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 23783 A (SMITHKLINE BEECHAM PLC) 8 August 1996 cited in the application see page 1; claim 1; examples 54,55,137-139	1,8-11
P,X	WO 97 48700 A (SMITHKLINE BEECHAM PLC) 24 December 1997 cited in the application see claims	1,8-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 1998	24/09/1998

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)